REMARKS

Reconsideration and withdrawal of the objections to the specification, and objections and rejection of the claims, in view of the amendments and remarks herein, is respectfully requested. Claims 1, 21 and 43 are amended, and claims 8, 47 and 60 are canceled; as a result, claims 1-7, 9-46 and 48-59 are now pending in this application. The amendments are intended to advance the application and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the above-referenced application.

The Examiner requests that Applicant distinctly identify by page and line number with a concise explanation of the relevance any statements within a citation directly applicable to the instantly claimed invention. Applicant asks that the Examiner clarify this request, e.g., what is "a citation directly applicable to the instantly claimed invention", as Applicant has submitted Forms 1449 in compliance with the duty imposed by 37 C.F.R. § 1.56, and in accordance with 37 C.F.R. §§ 1.97 *et. seq.*, and the Examiner has initialed and returned those Forms 1449.

The Examiner objected to the specification under 35 U.S.C. § 112, first paragraph as 1) each of "doxorubicin", "doxyrubicin" and "doxil" may be abbreviated by "DOX", and so the specification must clearly and explicitly identify "doxorubicin", "doxyrubicin" and "doxil" throughout the disclosure, e.g., Figures 7, 13, 17, 18, and 19 do not identify the "DOX" compound; 2) pages 80, 82 and 110 do not specify registered trademarks; 3) the units (DF* and mU) in Table 2 (page 84) are not defined in the table or disclosed in the working example; 4) at page 19 the specification discloses that Figure 4B tabulates luciferase activity in HeLa cells infected rAAV, "and co-administration of..., or a combination of LLnL and doxorubicin". However, none of the figure legends of Figures 4A-E identify data from the combined use of LLnL and doxorubicin; 5) Figure 7 does not disclose the RLU being measured; 6) the data presented in Figure 6C, and the data presented in the panels of Figures 8-11 and 13, are not disclosed in the specification; and 7) the data presented in Figure 17 are not disclosed in the specification.

The amendments to the specification address bases 2), 4), and 6) of the objection.

With regard to the use of "doxorubicin" and "doxyrubicin" in the specification, those terms are synonymous.

Although it is disclosed that the bioavailability of DOXIL® to cell culture cells is unclear, as the active ingredient in DOXIL® is doxorubicin, in the context of the particular data disclosed in the specification (*in vitro* versus *in vivo*), the use of "DOX" in the specification is clear.

The units "ng/nL" and "mU" in Table 2 relate to the amount of Factor VIII (in ng/nL or mU/mL) in animals determined using an ELISA or Coatest (known methods, see page 82 in the specification, and IMUBIND® Elisa kit brochure and abstract for Gnatenko et al., Br. J. Hemato., 104:27 (1999) and Dinesen et al. (Thromb. Res., 31:707 (1983) (a copy of each is enclosed)).

With respect to the identity of "RLU" in Figure 7, the Examiner is requested to consider Example 4 in the specification which discloses a luciferase-based assay. The Examiner is requested to note that the results from such an assay are routinely reported as relative luminescence units.

It is Applicant's position that the Brief Description of Figure 17 in conjunction with Figure 17 as filed provides a clear disclosure of the data in each panel of Figure 17. Further details are requested of the Examiner on which data in Figure 17 are not clear.

Therefore, withdrawal of the objections to the specification under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 2, 9-15, 17-20, and 44 were objected to as being not germane to the claimed method. First, the Examiner has not cited a statute, or a C.F.R. or M.P.E.P. section, as a basis for the objection. Nevertheless, to be responsive, the Examiner is requested to consider that as claim 1 (on which claims 2, 9-15, and 17-20 depend), and claim 43 (on which claim 44 depends), recite the use of a rAAV, and claims 2, 9-15, 17-20 and 43 are directed to rAAV structure, claims 2, 9-15, 17-20 and 44 are appropriate.

The 35 U.S.C. § 112, Second Paragraph, Rejections

Claims 4-7, 28, 46, and 54 were rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. In particular, the Examiner asserts that 1) claims 4 and 46 recite "cellular uptake of rAAV" in reference to a cellular function modified by exposure to a second (claim 46) or third (claim 4) agent, and that there is insufficient antecedent basis for "cellular uptake of rAAV"; 2) claims 5-7 recite "corresponding" in reference to a mammalian cell that has been contacted with the rAAV and one or more agents, however, neither the claims nor the specification define the

term "corresponding"; and 3) claims 28 and 54 are indefinite as neither the claims nor the specification define the term "rAAV processing". These rejections are respectfully traversed.

It is Applicant's position that claims 4 and 46 are in compliance with § 112(2) as those claims recite "further comprising contacting".

It is also Applicant's position that claims 5-7 are clear as the comparison is between a mammalian cell contacted with rAAV and at least two agents and a mammalian cell contacted with rAAV and one of those agents or a mammalian cell contacted with rAAV. Thus, the same type of mammalian cell is employed in that comparison.

With respect to AAV "processing" in a cell, the specification discloses various steps in the AAV life cycle at page 7, lines 23-27, page 11, lines 6-11, and page 12, lines 13-15. Therefore, the phrase "rAAV processing" in the claims is clear.

Claims 1-2, 4-24, 28, 43-44, 46-50, 54, and 60 were also rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. Specifically, the Examiner asserts that the omitted elements are the correlation between the identity and structural limitations of each composition/agent and the recited cellular effect achieved by that agent. As this rejection may be maintained with respect to the pending claims, it is respectfully traversed.

As amended, the claims are directed to a method to enhance rAAV transduction of a mammalian cell, which method employs at least two agents, where one agent is a chemotherapeutic, a lipid lowering agent, an antibiotic or a food additive and a second agent inhibits proteosome proteolytic activity, or where one agent is epoxomicin, doxorubicin, DOXIL®, daunorubicin, idarubicin, epirubicin, aclarubicin, simvastatin or tannic acid.

Therefore, withdrawal of the § 112(2) rejections is respectfully requested.

The 35 U.S.C. § 112, First Paragraph, Rejections

Claims 1-2, 4-24, 28, 43-44, 46-50, 54, and 60 were rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description. The Examiner asserts that at issue are a) the identity and structure of the agent that "alters cellular uptake of rAAV", b) the identity and structure of the agent that "modulates rAAV processing in the cell," and c) the number of species

of agents that alter cellular uptake of rAAV or modulate rAAV processing in the cell. This rejection is respectfully traversed.

As amended, the claims are directed to the use of a chemotherapeutic, a lipid lowering agent, an antibiotic or a food additive and a second agent that inhibits proteosomes proteolytic activity, or the use of two agents where one agent is epoxomicin, doxorubicin, DOXIL®, daunorubicin, idarubicin, epirubicin, aclarubicin, simvastatin or tannic acid. The specification describes a variety of chemotherapeutics, lipid lowering agents, antibiotics and/or a food additive. Therefore, one skilled in the art would recognize that Applicant was in possession of the necessary common attributes or features of the elements possessed by members of the genus.

With regard to agents that "alter cellular uptake of rAAV", see page 4 of the specification, which discloses that agents that alter cellular uptake of rAAV were known prior to Applicant's filing. Applicant need not describe what is well-known to the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94-95 (Fed. Cir. 1986).

Therefore, withdrawal of the written description rejection under § 112(1) is respectfully requested.

Claims 1-2, 4-24, 28, 43-44, 46-50, 54, and 60 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Specifically, the Examiner asserts that 1) the breadth of the claims is exceptionally large for encompassing methods of enhancing the transduction of an enormous genus of rAAV to an enormous genus of mammalian cells (both organisms and physiological cell types), wherein the transduction may occur *in vitro*, *ex vivo* or *in vivo*, using of an enormous genus of structurally diverse agents recited to perform a broad genus of distinctly different cell biological effects so as to enhance rAAV transduction in the target cell; 2) given the limited teachings in the art regarding the co-administration of two or more compounds designed to specifically alter particular cell biological processes to intentionally enhance rAAV transduction of an enormous genus of mammalian cell types *in vitro*, *ex vivo* and *in vivo*, one of ordinary skill in the art would reasonably conclude that a high degree of unpredictability regarding an *a priori* determination that any specific compound will enhance viral transduction much less significant unpredictability for any two agents to yield an additive interaction to enhance viral transduction; 3) there is a clear contradiction with regard to the properties of doxorubicin and DOXIL® in view of Yan et al. (J. Virol., 78:2863 (2004)) and of the elected

species doxorubicin and DOXIL® in claims 43 and 60 which are recited to not be an inhibitor of proteosome proteolytic activity; and 4) the specification fails to disclose agents that "alter cellular uptake of rAAV". Based on that, the Examiner concludes that one of skill in the art would engage in undue experimentation to practice the claimed invention. This rejection, as it may be maintained with respect to the pending claims, is respectfully traversed.

It is well-settled that it is not necessary that a patent applicant have prepared and tested all the embodiments of his invention in order to meet the requirements of § 112. In re Angstadt, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). Furthermore, enablement is not precluded by the necessity for some experimentation, such as routine screening. The key word is "undue" not "experimentation." In re Angstadt, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976). In fact, a considerable amount of experimentation is permissible if it is merely routine, or the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should take. Ex parte Jackson, 217 U.S.P.Q. 804, 807 (Bd. App. 1982). Thus, if Applicant's invention is disclosed so that one of ordinary skill in the art can practice the claimed invention, even if the practice of the invention by the art worker includes routine screening or some experimentation, Applicant has complied with the requirements of 35 U.S.C. § 112, first paragraph. In re Angstadt, 190 U.S.P.Q. 214 (C.C.P.A. 1976); Ex parte Jackson, 217 U.S.P.Q. 804 (Bd. App. 1982).

As amended, the claims are directed to the use of at least two agents to enhance AAV transduction, where one agent is a chemotherapeutic, a lipid lowering agent, an antibiotic or a food additive and a second agent inhibits proteosomes proteolytic activity, or where one agent is epoxomicin, doxorubicin, DOXIL®, daunorubicin, idarubicin, epirubicin, aclarubicin, simvastatin or tannic acid.

With regard to the genus of rAAV and genus of mammalian cells, it is Applicant's position that it is well within the skill of the art, in view of Applicant's disclosure, to contact various isolates of AAV and a wide variety of mammalian cells with two or more agents, including the recited agent(s), to determine whether the agents enhance rAAV transduction. It is Applicant's specification that provides the requisite predictability that certain agents together enhance rAAV transduction.

With regard to basis 3) of the rejection, the Examiner is requested to consider that the present specification discloses that "proteosome modulating agents" do not include agents that inhibit the proteolytic activity of the proteosome, that doxorubicin may facilitate viral binding to the proteasome and/or subsequent transportation into the nucleus in contrast to proteasome inhibitors such as LLnL and Z-LLL that more significantly inhibit core proteolytic activity of the proteasome, and that the combined use of agents that individually have different or overlapping properties that alter rAAV transduction, as well as agents with similar or identical properties, can result in an additive and/or synergistic effect (pages 7 and 9). Further, in response to the election of two species from an agent that is epoxomicin, doxorubicin, doxil, daunorubicin, idarubicin, epirubicin, aclarubicin camptothecin, simvastatin, tannic acid, cisplatin, LLnL or Z-LLL, in the Response mailed March 19, 2007, Applicant provisionally elected, with traverse, species doxil and LLnL and indicated that claims 1-32 and 43-60 read on specie doxil and specie LLnL. Note that claim 43, prior to amendment, was directed to a method comprising contacting mammalian cells with at least one agent.

As discussed above, agents that "alter cellular uptake of rAAV" were known prior to Applicant's filing. Applicant need not describe what is well-known to the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 231 U.S.P.Q. 81, 94-95 (Fed. Cir. 1986).

Accordingly, withdrawal of the § 112(1) enablement rejection is respectfully requested.

The 35 U.S.C. § 102 Rejections

Claims 43, 47, 50, 54, and 60 were rejected under 35 U.S.C. § 102(a) as being anticipated by Schwarzbach et al. (Int. J. Oncology, 20:1211 (2002)). Claims 43, 47, 50, 54, and 60 were further rejected under 35 U.S.C. § 102(b) as being anticipated by Yalkinoglu et al. (Int. J. Cancer, 45:1194 (1990)). Claims 1-2, 5-7, 9, 16, 18, 21-23, 28, 43-44, 46, 48, 50, and 54 were rejected under 35 U.S.C. § 102(b) as being anticipated by Duan et al. (J. Clin. Invest., 105:1573 (2000)). Claims 1-2, 4-7, 9, 18, 22, 28, 43-44, 46, 50, and 54 were also rejected under 35 U.S.C. § 102(b) as being anticipated by Tenenbaum et al. (Gene Therapy, 6:1045 (1999)). These rejections are respectfully traversed.

Schwarzbach et al. disclose that the cytotoxic effect of doxorubicin treatment (for 12-24 hours) of human sarcoma cell lines was enhanced by subsequent infection with AAV-2 (abstract

and page 1212). There is no mention in Schwarzbach et al. of the effect doxorubicin had on AAV transduction.

Yalkinoglu et al. disclose infection of CHO cells with AAV-2 and, 6 hours later, a 2 hour treatment with a carcinogen (MNNG) (page 1196). 72 hours after carcinogen treatment, it is disclosed that the cells were analyzed for DNA amplification or trypsinized and seeded for selection in methotrexate (MTX)- or adriamycin (ADR)-containing media (page 1196). It is also disclosed that infection of cells with AAV-2 prior to treatment with MNNG markedly inhibited carcinogen-induced drug resistance, while infection of AAV alone did not exert any effect (abstract). There is no mention in Yalkinoglu et al. that MNNG, MTX or ADR enhanced AAV transduction.

Neither Schwarzbach et al. nor Yalkinoglu et al. teach contacting mammalian cells with at least two agents that together at least additively enhance rAAV transduction.

Duan et al. disclose that the combined effects of EGTA (a chelating agent) and LLnL on AAV transduction might be due to reduced degradation of internalized virus and an increased rate of endocytosis, and that the combination enhanced the amount of virus internalized from apical surfaces (pages 1582 and 1583). It is also disclosed that LLnL does not alter AAV binding to cell surfaces or internalization (page 1581). Thus, it is likely that EGTA altered AAV binding to cell surfaces or internalization.

Although Duan et al. disclose that EGTA pretreatment may enhance the activity of LLnL or Z-LLL at the apical surface of bronchial epithelial cells, Duan et al. do not disclose the use of two or more agents to enhance rAAV transduction of a mammalian cell, where one of the agents is a chemotherapeutic, lipid lowering agent, antibiotic or food additive and another agent that is an inhibitor of proteosome proteolytic activity or where one of the agents is epoxomicin, doxorubicin, DOXIL®, daunorubicin, idarubicin, epirubicin, aclarubicin, simvastatin or tannic acid.

Tenenbaum et al. disclose that 293 sonicated extracts stimulated rAAV-mediated transduction of HeLa and 293 cells.

Tenenbaum et al. do not disclose contacting mammalian cells with a chemotherapeutic, a lipid lowering agent, an antibiotic or a food additive and a second agent that inhibits proteosome proteolytic activity, or contacting mammalian cells with at least two agents, where one agent is

epoxomicin, doxorubicin, DOXIL®, daunorubicin, idarubicin, epirubicin, aclarubicin, simvastatin or tannic acid.

Thus, withdrawal of the § 102 rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop Amendment, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 14 day of August 2007.

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